



## COMPARISON OF SODIUM BICARBONATE AND NACL 0.9% MOUTHWASH IN PREVENTING ORAL MUCOSITIS IN CHILDREN WITH HEMATOLOGIC MALIGNANCY UNDERGOING CHEMOTHERAPY

<b>Christina Hasibuan</b>	Department of Child Health, Medical School – Universitas Sumatera Utara, Medan – Indonesia
<b>Chairul Yoel</b>	Department of Child Health, Medical School – Universitas Sumatera Utara, Medan – Indonesia
<b>Josia Ginting*</b>	Department of Internal Medicine, Medical School – Universitas Sumatera Utara, Medan – Indonesia*Corresponding Author
<b>Karina Sugih Arto</b>	Department of Child Health, Medical School – Universitas Sumatera Utara, Medan – Indonesia
<b>Ayodhia Pitaloka Pasaribu</b>	Department of Child Health, Medical School – Universitas Sumatera Utara, Medan – Indonesia
<b>Bidasari Lubis</b>	Department of Child Health, Medical School – Universitas Sumatera Utara, Medan – Indonesia

### ABSTRACT

**Background:** Oral health care is recommended for preventing oral mucositis or the progression of oral mucositis itself, one of its component is mouthwash. Sodium bicarbonate (SB) or NaCl 0.9% is still recommended, which one is more effective remains to be established.

**Methods:** In April 2018 until December 2018, we conducted a prospective open-label randomized trial comparison of 4 weeks oral health care with NaCl 0.9% and SB mouthwash in pediatric patients with hematologic malignancy undergoing chemotherapy. Oral mucositis was assessed with WHO Oral Toxicity Scale and all patients were confirmed not having oral mucositis before the intervention. Data were analyzed using SPSS ver 20.0. We performed survival analysis with log rank test and comparison between groups were made by Chi square test, Fisher exact test, and Mann-Whitney U test where appropriate. Significance level of  $P < .05$  and 95% CI.

**Result:** Sixty-nine patients were included, 35 patients received SB and 34 patients received NaCl 0.9%. There were no significant difference in patients characteristics at baseline between two groups. From Kaplan Meier curve, there was no significant difference between the two groups for mean onset of oral mucositis in SB (11.32 days, median 10 days) and NaCl 0.9% group (11.93 days, median 11 days) ( $P=.763$ ). Duration of oral mucositis was significantly different, in SB and NaCl 0.9% group were 4.86 days and 7.39 days respectively ( $P=.004$ ). At the end of this study, incidence of oral mucositis was 47.8% in SB group and 48% in NaCl 0.9% group ( $P=.768$ ).

**Conclusion:** SB was not superior compared to NaCl 0.9% as mouthwash for preventing oral mucositis, but duration of oral mucositis was shorter in SB group.

**KEYWORDS :** oral mucositis; mouthwash; children; chemotherapy

### INTRODUCTION

Oral mucositis is an inflammation of the oral cavity and often found in patient receiving chemotherapy and/or radiotherapy (Eilers & Million, 2011; Lala et al., 2014). The incidence of oral mucositis in overall cancer population ranges between 30-80% and there is a 40% relative risk of developing oral mucositis following many standard chemotherapy regimens (Peterson, 2006; European Oncology Nursing Society, 2007). Study in Egypt and India reported that the most common oral complication associated with chemotherapy agent's cytotoxicity in children undergoing chemotherapy was oral mucositis, which was 53.3% and 58.1% respectively (El-Housseiny et al., 2007; Gandhi et al., 2017). Study in Yogyakarta, conducted in children with cancer aged 31 days to 15 years old, found high incidence of oral mucositis which was 42.2% (Mulatsih et al., 2008). Oral mucositis can increase patient's morbidity and mortality, therefore oral health care is recommended in all patient undergoing chemotherapy and/or radiotherapy (Cheng et al., 2015; Elting et al., 2004).

There are many study about oral health care for oral mucositis related to anticancer therapy that had been conducted. The most interesting part of oral care that had been major issue to be studied is mouthwash. Based on Multinational Association of Supportive Care in Cancer and The International Society of Oral Oncology (MASCC/ISOO), United Kingdom Oral Mucositis in Cancer Group, and Oncology Nursing Society bland rinse such as sodium bicarbonate or NaCl 0.9% are still recommended for oral health care (Eilers & Million, 2011; Lala et al., 2014; UK Oral Mucositis in Cancer Group, 2015). There were many mouthwash that had been studied, some of

them are iseganan, sucralfate, chlorhexidine, povidone iodine, and antifungal agent, for preventing oral mucositis in patient undergoing chemotherapy but MASCC/ISOO guidelines in 2014 do not suggested those agents as routine mouthwash in patient undergoing chemotherapy. Therefore, the first choice of mouthwash for basic oral health care are sodium bicarbonate, NaCl 0.9%, or mixture of both agents still (Lala et al., 2014; UK Oral Mucositis in Cancer Group, 2015; UKCCSG-PONF Mouth Care Group, 2006). Study on effectiveness of sodium bicarbonate and NaCl 0.9% are limited, recent study in Tamilnadu in patients with oropharyngeal cancer reported that sodium bicarbonate mouthwash is better than NaCl 0.9% in reducing severity of oral mucositis (Arunkumar, 2017). Further study on effectiveness in both agents for preventing oral mucositis or the progression of oral mucositis is needed, especially in pediatric population.

### METHODS

We performed a prospective, open-label, randomized study comparing NaCl 0.9% and sodium bicarbonate (SB) mouthwash for preventing oral mucositis in children with hematologic malignancy undergoing chemotherapy at Hospital of Haji Adam Malik, Medan. Participants were recruited from patients who admitted hematology oncology division and diagnosed with hematologic malignancy such as acute lymphoblastic leukemia (ALL), acute myeloblastic leukemia (AML), Hodgkin lymphoma (HL), and non Hodgkin lymphoma (NHL).

Study was conducted from April 2018 until December 2018. Patients who met the following criteria were included: (1) newly diagnosed

patient with hematological malignancy; (2) had never been treated with chemotherapy; (3) patients and/or parents understand and commit to the oral health care procedure. Patient were excluded from the study if they had any of the following conditions: (1) oral mucositis present before chemotherapy; (2) patients in the critical condition; (3) patient in immunocompromised condition aside from patient's current disease or side effect of the therapy. Written inform consent was obtained from patients or their attending relatives before enrollment. The study was approved by the Ethics Committee of Faculty of Medicine University of Sumatera Utara, Medan.

The sample size of the study was calculated using the formula for unpaired categorical comparative analytical study with an alpha value .05 and power of 80% (Dahlan, 2016). Thirty-four individuals were required per group.

**MEASUREMENT**

Scoring oral mucositis with WHO Oral Toxicity Scale Oral mucositis, including its severity, was evaluated using WHO Oral Toxicity Scale. This instrument was used to describes oral mucositis related to the toxicity of cancer treatment. WHO Oral Toxicity Scale rate the overall status of the mouth relative to the clinically observed mucosal appearance, severity of the patient's pain, and in some instances the patient's functional capabilities relative to patient's oral status (UKCCSG-PONF Mouth Care Group, 2006; WHO, 1979). WHO Oral Toxicity Scale is widely used, analysis of approximately 400 trials, as a component of the evidence-based review for the clinical practice guidelines, determined that most of the study using the WHO Scale (38%) or National Cancer Institute-Common Toxicity Criteria (43%) (Sonis et al., 2004).

The severity of oral mucositis is graded from 0 (no mucositis) to 4 (alimentation not possible). The criteria for scoring severity of mucositis are as follows: 0 = no change; 1 = localized erythema of oral mucosa; 2 = diffuse erythema, discrete erosive lesions, can eat solid foods; 3 = diffuse erythema, discrete erosive lesions, ulceration, requires liquid diet only; and 4 = multiple ulcers, necrosis of oral mucosa, alimentation not possible (WHO, 1979).

**NUTRITIONAL STATUS**

Assessment of patient's nutritional status using WHO 2006 growth chart for children aged < 5 years and CDC 2000 growth chart for children aged 5 – 18 years. Patients whose weight for height/length result in WHO 2006 growth chart > +1 standard deviation (SD) or CDC 2000 growth chart > 110% must be evaluated further based on Body Mass Index using WHO 2006 BMI chart for children aged < 2 years or CDC 2000 BMI chart for children aged 2 – 18 years. If patient with edema, ascites, and/or organomegaly, nutritional status was assessed with upper arm circumference (UKK Nutrisi dan Penyakit Metabolik, 2011).(see Appendix)

**ORAL HEALTH STATUS**

Patient was consulted to dental and oral health spesialist for evaluation whether there was acute infection or not before chemotherapy and also during chemotherapy if needed.

**MOUTHWASHES**

Sodium bicarbonate (SB) preparation consists of 2 grams sodium bicarbonate (4 tablets) which was changed into dry powdered form and placed in a airtight plastic bag. This preparation would be given to patients or their attending relatives. Sodium bicarbonate solution was made by mixing dry powdered sodium bicarbonate in 200 ml of sterile water just before doing oral health care protocol (Choi & Kim, 2012).

NaCl 0.9% was converted to powdered salt. Calculation of 154 mEq sodium per 1000 ml with valence of sodium 1 and atomic weight of sodium 23 was comparable to 17.26 grams of powdered salt in 1000 ml of sterile water or 3.45 gram of powdered salt in 200 ml of sterile water. Therefore, salt preparation will consists of 3.45 grams powdered salt which was placed in a airtight plastic bag and would

be given to patients or their attending relatives. Salt solution was made by mixing the salt preparation in 200 ml of sterile water just before doing oral health care protocol.

**PROCEDURE**

Patients who met the inclusion criteria was given inform consent and randomized for the allocation of each group. Patients was educated about the need for oral health care, oral complications related to cancer treatment, and how to do oral health care protocol (see Appendix) including methods of brushing and gargling. Data related to patient's identity, patient's anthropometric measurements, parents background, and oral health status were recorded in patient's data entry form; chemotherapy regimens and laboratory result were obtained from medical record. Monitoring was done everyday but there was 3 main points of measurement which were T0, T1, and T2. T0 was defined as starting point, before chemotherapy and treatment was given. T1 was referred to day 14 after chemotherapy and treatment was given. T2 was referred to day 28 after chemotherapy and treatment was given.

Condition of oral mucosa and oral health were evaluated everyday, the results would be recorded in observation sheets (see Appendix); whereas patient's anthropometric, nutritional status, chemotherapy regimens, and hematological parameters were evaluated everyweek. Primary outcome was incidence of oral mucositis.

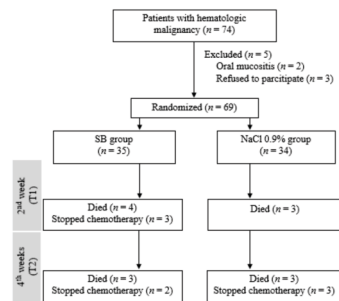
**STATISTICAL ANALYSIS**

All patients who were enrolled and randomly allocated to treatment were included in the analysis and analysed in the group to which they were randomized. All analysis performed using SPSS version 20.0. Comparison between groups were made by Chi square test, Fisher exact test, Mann-Whitney U test, and Student t test where appropriate. Efficacy after 4 weeks of follow up were assessed by Kaplan-Meier survival analysis with log rank test for statistical significance.

**RESULTS**

This study was followed by 69 patients with hematologic malignancy who underwent chemotherapy at Hospital of Haji Adam Malik, Medan and had met the inclusion criteria. Patients were divided into two groups, 35 patients received SB mouthwash and 34 patients received NaCl 0.9% for oral health care (Figure 1).

Patient's characteristics are presented in Table 1. Majority of patients in both groups were male and diagnosed with ALL. The age average between the two groups not significantly different (SB group mean 8.82, SD4.79; NaCl 0.9% group mean 9.32, SD 5.73; P=.806). The proportion of patients with severe malnutrition was greater in SB group than NaCl 0.9% group, 42.9% versus 29.4%, but if analyzed further there was no significant difference between the two groups (P=.295). The proportion of patients with poor oral health and absolute neutrophil count (ANC) < 1,500/uL in the two group were not different statistically (P=.911 and P=.714).



**Figure 1. CONSORT diagram**

Nutritional status, oral health, the severity of oral mucositis, and hematological parameters during and after treatment can be seen in Table 2. At initial assessment, before patients started chemotherapy and underwent oral health care (T0), each patient

was confirmed not having oral mucositis. Oral mucositis occurred in the 2<sup>nd</sup> week (T1), there were 65.5% patients with oral mucositis in SB group and 54.8% patients with oral mucositis in NaCl 0.9% group. We can also see that the highest grade of oral mucositis were at T1, which were 17.2% and 12.9% in SB and NaCl 0.9% group (Table 2).

**Table 1. Patient's characteristics at baseline**

Characteristics	SB group n = 35	NaCl 0.9% group n = 34
Gender, n (%)		
Male	23 (65.7)	25 (73.5)
Female	12 (34.3)	9 (26.5)
Age, mean (SD), year	8.82 (4.79)	9.32 (5.73)
Parents education, n (%)		
Primary	3 (8.0)	2 (5.9)
Junior high	8 (22.9)	5 (14.7)
Senior high	14 (40.0)	13 (38.2)
University	10 (29.1)	14 (41.2)
Diagnosis, n (%)		
ALL	25 (71.4)	25 (73.5)
AML	4 (11.4)	4 (11.8)
HL	1 (2.9)	2 (5.9)
NHL	5 (14.3)	3 (8.8)
Chemotherapy regimens, n (%)		
Citarabine	4 (11.4)	4 (11.8)
Etoposide	1 (2.9)	2 (5.9)
Metothrexate/vincristine	25 (71.4)	25 (73.5)
Metothrexate/vincristine/citara bine	5 (14.3)	3 (8.8)
Nutritional status, n (%)		
Severe malnutrition	15 (42.9)	10 (29.4)
Mild malnutrition	13 (37.1)	19 (55.9)
Normal	7 (20.0)	5 (14.7)
Oral health, n (%)		
Poor	16 (45.7)	16 (47.1)
Good	19 (54.3)	18 (52.9)
Hemoglobin, mean (SD), g/dl	7.27 (2.58)	7.58 (2.03)
Hematocrit, mean (SD), %	22.95 (8.72)	23.42 (6.53)
Leukocyte, mean (SD), 10 <sup>3</sup> /uL	25,14 (40,87)	55,16 (119,19)
Trombocyte, mean (SD), 10 <sup>3</sup> /uL	66,64 (79.69)	107,17 (108,65)
ANC, n (%)		
< 1,500/uL	17 (48.6)	17 (50.0)
≥ 1,500/uL	18 (51.4)	17 (50.0)

Abbreviations: ANC, absolute neutrophil count; ALL, acute lymphoblastic leukemia; AML, acute myeloblastic leukemia; HL, Hodgkin lymphoma; NHL, non Hodgkin lymphoma; SB, sodium bicarbonate; SD, standard deviation

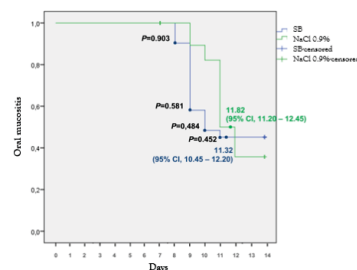
**Table 2. Comparison of observations at the 2<sup>nd</sup> week and 4<sup>th</sup> week after treatment**

Observations	SB group	NaCl 0.9% group	P
Nutritional status, n (%)			
T1 Severe malnutrition	10 (35.7)	5 (16.1)	.454 <sup>a</sup>
Mild malnutrition	15 (53.6)	13 (41.9)	
Normal	3 (10.7)	13 (41.9)	
T2 Severe malnutrition	6 (26.1)	11 (44.0)	.436 <sup>a</sup>
Mild malnutrition	13 (56.5)	9 (36.0)	
Normal	4 (17.4)	5 (20.0)	
Oral health, n (%)			
T1 Poor	10 (35.7)	12 (38.7)	.969 <sup>a</sup>
Good	18 (64.2)	19 (61.3)	
T2 Poor	5 (21.7)	5 (20.0)	.623 <sup>b</sup>
Good	18 (7.3)	20 (80.0)	

Oral mucositis, n (%)			
T1 Grade 0	10 (35.7)	14 (45.2)	.399 <sup>a</sup>
Grade 1	14 (50.0)	13 (41.9)	
Grade 2	4 (14.3)	4 (12.9)	
T2 Grade 0	12 (52.2)	13 (52.0)	.768 <sup>a</sup>
Grade 1	11 (47.8)	12 (48.0)	
Hemoglobin, mean (SD), g/dl			
T1	8.89 (2.18)	9.68 (2.77)	.223 <sup>c</sup>
T2	10 (2.05)	10.76 (2.11)	.210 <sup>c</sup>
Hematocrit, mean (SD), %			
T1	27.06 (6.72)	29.53 (8.39)	.216 <sup>c</sup>
T2	30.06 (6.45)	32.39 (6.76)	.223 <sup>c</sup>
Leukocyte, mean (SD), 10 <sup>3</sup> /uL			
T1	17,41 (22,86)	29,1 (67,03)	.544 <sup>c</sup>
T2	11,41 (10,62)	11,5 (23,76)	.138 <sup>c</sup>
Trombocyte, mean (SD), 10 <sup>3</sup> /uL			
T1	85,36 (96,95)	196,1 (178,23)	.018 <sup>c</sup>
T2	122,99 (119,12)	241,62 (198,82)	.056 <sup>c</sup>
ANC, n (%)			
T1 < 1,500/uL	15 (53.6)	13 (41.9)	.371 <sup>b</sup>
≥ 1,500/uL	13 (46.4)	18 (58.1)	
T2 < 1,500/uL	9 (39.1)	11 (44.0)	.620 <sup>b</sup>
≥ 1,500/uL	14 (60.9)	14 (56.0)	

<sup>a</sup>Chi Square, <sup>b</sup>Fischer exact, <sup>c</sup>Mann-Whitney. Abbreviations: ANC, absolute neutrophil count; SB, sodium bicarbonate; SD, standard deviation

Kaplan-Meier survival curve was used to determine if there was significant difference in onset of oral mucositis between the two groups. The mean onset of oral mucositis in patients receiving SB and NaCl 0.9% mouthwash were 11.32 days (median 10 days) and 11.93 days (median 11 days). For all patients, mean onset of oral mucositis was 11.61 days (median 11 days). Using log rank test, we found that there was no association between types of mouthwash for oral health care and onset of oral mucositis (log rank 0.024; P=.877). Mann-Whitney U test showed that there was significant difference in duration of oral mucositis in SB group (4.86 days) and NaCl 0.9% (7.39 days) (P=.0004). We also used Chi square test and Fisher exact test to determined whether the incidence of oral mucositis had significant difference between and within groups after 4 weeks of treatment, but the result showed there were no significant difference (Table 3).



**Figure 2. Kaplan-Meier survival analysis for oral mucositis from T0 until T1. Abbreviation: SB, sodium bicarbonate**

**Table 3. Proportion of oral mucositis after 2 and 4 weeks of treatment**

Oral mucositis	Mouthwash		P
	SB	NaCl 0.9%	
At 2 <sup>nd</sup> week, n (%)			
Yes	18 (64.3)	17 (54.8)	0.399 <sup>a</sup>
No	10 (35.7)	14 (45.2)	
At 4 <sup>th</sup> week, n (%)			

<b>Yes</b>	<b>11 (47,8)</b>	<b>12 (48.0)</b>	<b>0.768<sup>a</sup></b>
<b>No</b>	<b>12 (52,2)</b>	<b>13 (52.0)</b>	
<b>P</b>	<b>0.180<sup>b</sup></b>	<b>1.000<sup>b</sup></b>	

<sup>a</sup>Chi Square, <sup>b</sup>Fischer exact. Abbreviation: SB, sodium bicarbonate

**DISCUSSION**

Oral mucositis remains an issue in patients receiving chemotherapy and/or radiotherapy. The incidence of oral mucositis varies between 30-80% in overall cancer population (Peterson, 2006). In our study, oral mucositis occurred in the 2<sup>nd</sup> weeks of treatment with overall incidence of oral mucositis was about 59.5%. This numbers was slightly higher than the previous studies (El-Housseiny et al., 2007; Gandhi et al., 2017), it may happened because the population's target of each study were different. This study only included pediatric patient with hematologic malignancy, such as acute lymphoblastic leukemia, acute myeloblastic leukemia, Hodgkin lymphoma, and non Hodgkin lymphoma, whereas study in India included not only patients with hematologic malignancy but also patients with solid tumor and study in Egypt only evaluated patient with oral mucositis grade 2 or more (Housseiny et al., 2007; Gandhi et al., 2017).

Overall, the mean onset of oral mucositis was 11.61 days (median 11 days). Based on literature, the mucotoxic effects of chemotherapeutic agents tends to be acute, developing within a week after drug administration and reaching a peak within 2 weeks (Subramaniam, 2008). It can be seen in Figure 2 that there was no association between types of mouthwash for oral health care and onset of oral mucositis. Also, there was no significant difference in the severity of oral mucositis and in the incidence of oral mucositis in both groups after 4 weeks of treatment (Table 2 and Table 3). Previous studies about the effectiveness of NaCl 0.9% and sodium bicarbonate were limited but there were two study, in New York and Tamilnadu, that compared NaCl 0.9% and sodium bicarbonate (Arunkumar, 2017; Kenny, 1990). Study in Tamilnadu reported sodium bicarbonate more effective in reducing the severity of oral mucositis and patients in sodium bicarbonate group had delayed onset of oral mucositis, but this study was done in adult patients with oropharyngeal cancer (Arunkumar, 2017). Other study in New York reported that incidence of oral mucositis was lower in patients who received NaCl 0.9% mouthwash, unfortunately this study had small sample size and different population's target (Kenny, 1990). Therefore, effectivity of NaCl 0.9% and sodium bicarbonate in preventing oral mucositis still difficult to conclude.

Although the incidence of oral mucositis in both group was not significant different statistically, we can see from Table 2 and Table 3 that the decreasing incidence of oral mucositis was higher in SB group. Also, the duration of oral mucositis was shorter in SB group. These may occur because sodium bicarbonate had effect in increasing saliva's pH so the acidity in oral cavity can be neutralized and in the end colonization of acid resistant bacteria can be prevented. On the other hand, NaCl 0.9% doesn't had biologically active compound (McGuire, 2013; Harris, 2004; Farah, 2009). Until now, no studies were done in evaluating the effect of sodium bicarbonate compared to NaCl 0.9% mouthwash in the duration of oral mucositis. Therefore, this study can be a starting point for developing future researches. Further study in pediatric population with larger sample size, longer follow up, and more detail instruments in assessing oral mucositis is needed.

**CONCLUSION**

Sodium bicarbonate was not superior compared to NaCl 0.9% as mouthwash for preventing oral mucositis but the duration of oral mucositis was shorter in patient received sodium bicarbonate mouthwash.

**ACKNOWLEDGMENTS**

We thank all colleague, the patients, and their familie who participated in this study.

**ORAL HEALTH CARE PROTOCOL USING SODIUM BICARBONATE OR NaCl 0.9% MOUTHWASH<sup>11,17</sup>**

**Assessment:**

inspect the mucosa of the lips, bucal mucosa, gums, tongue, palate, and the floor of the mouth. Record in observation sheet.

**Preparation:**

SB mouthwash is made by mixing one package of sodium bicarbonate preparation in 200 ml of sterile water; or NaCl 0.9% mouthwash is made by mixing one package of salt preparation in 200 ml of sterile water.

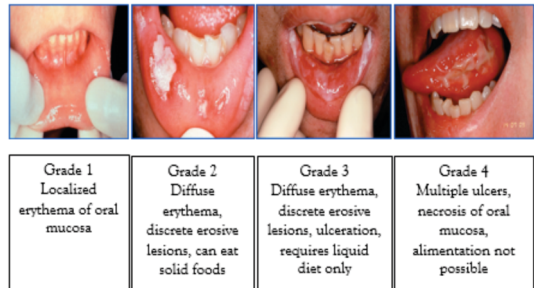
**Implementation:**

1. Gargling is done after breakfast, lunch, dinner, and before sleep at night
2. Prepare a timepiece so that the rinsing time can be calculated at least 30 seconds
3. Rinse oral cavity with SB mouthwash by moving the solution in the mouth to reach all the mucous membrane of the mouth
4. After finishing, dispose the mouthwash
5. Record in observation sheet how many times patients did oral health care in a day

Note: patients or their attending relatives are also educated to do brushing, twice a day. For children under 6 years old, brushing teeth should be assisted by their attending relatives. In infants, you can use a soft damp towels, done 2-3 times a day

**OBSERVATION SHEET**

**WHO Oral Toxicity Scale<sup>7,14</sup>**



Grade	Week....							Week....						
	1	2	3	4	5	6	7	1	2	3	4	5	6	7
0														
1														
2														
3														
4														

**OBSERVATION SHEET**

**Checklist for Protocol**

Name/ Medical record :  
 Age :  
 Diagnosis :

Time	Week....							Week....						
	1	2	4	5	6	7	1	2	3	4	5	6	7	
After breakfast														
After lunch														
After dinner														
Before Sleep at night														
Note														

**REFERENCES**

1. Eilers, J., & Million, R. (2011). Clinical update: Prevention and management of oral mucositis in patient with cancer. *Seminars in Oncology Nursing*, 27, e1-e16.

2. Lalla, R. V., Bowen, J. M., Barasch, A., Elting, L., Keefe, D. M., ...Elad, S. (2014). MASCC/ISOO clinical practice guidelines for management of mucositis secondary to cancer therapy. *Supportive Care in Cancer*, 120, 1453-61.
3. Peterson, D.E. (2006). New strategies for management of oral mucositis in cancer patient. *Journal of Supportive Oncology*, 4, 009-13.
4. European Oncology Nursing Society. (2007). Section 4 Oral mucositis guidelines: Guidelines Implementation Toolkit.
5. El-Housseiny, A., Saleh, S., El-Masry, A., & Allam, A. (2007). Assessment of oral complications in children receiving chemotherapy. *Journal of Clinical Pediatric Dentistry*, 31, 267-73.
6. Gandhi, K., Datta, G., Ahuja, S., Saxena, T., & Datta, A. G. (2017). Prevalance of oral complications occurring in a population of paediatric cancer patients receiving chemotherapy. *International Journal of Clinical Pediatric Dentistry*, 10, 166-71.
7. Mulatsih, S., Sri, A. S., Purwantika, Y., & Christine, J. (2008). Kejadian dan Tatalaksana Mukositis pada Pasien Keganasan di RSUP Dr. Sardjito, Yogyakarta. *Sari Pediatri*, 10, 230-5.
8. Cheng, K. K., Lee, V., Li, C. H., Yuen, H. L., ...Epstein, J. B. (2013). Impact of oral mucositis on short-term clinical outcomes in pediatric and adolescent patients undergoing chemotherapy. *Supportive Care in Cancer*, 8, 2145-52.
9. Elting, L. S., Cooksley, C., Chambers, M., Cantor, S. B., Manzullo, E., & Rubenstein, E. B. (2004). The burdens of cancer therapy. *Cancer*, 98, 1531-9.
10. UK Oral Mucositis in Cancer Group. (2015). Mouth care guidance and support in cancer and palliative care. United Kingdom: UKOMiCG.
11. UKCCSG-PONF Mouth Care Group. (2006). Mouth care for children and young people with cancer: Evidence-based guideline.
12. Arunkumar, C., Srinivasan, V., Balaji, N., & Indumathi, G. (2017). Comparison of effects of sodium bikarbonate and normal saline mouthwash for management of radiation induced mucositis in patients undergoing radiation for oropharyngeal cancer. *International Journal of Current Research*, 9, 54129-34.
13. Dahlan MS. (2016). Langkah-langkah membuat proposal penelitian. Jakarta: Sagung Seto.
14. WHO. (1979). Handbook for reporting results of cancer treatment. Geneva: Wo Health Organisation.
15. Sonis, S. T., Elting, L. S., Keefe, D., Peterson, D. E., Schubert, M., ...Rubenstein, E. B. (2004). Perspective on cancer therapy induced mucosal injury: pathogenesis, measurement, epidemiology, consequences for patients. *Cancer*, 100, 1995-2025.
16. UKK Nutrisi dan Penyakit Metabolik. (2011). Rekomendasi ikatan dokter anak Indonesia. Jakarta: Ikatan Dokter anak Indonesia.
17. Choi, S. E., & Kim, H. S. (2012). Sodium bikarbonate solution versus chlorhexidine mouthwash in oral care of acute leukemia patients undergoing induction chemotherapy: A randomized control trial. *Korean Society of Nursing Science*, 6, 60-6.
18. Subramaniam, P., Babu, K. L., & Nagaratha, J. (2008). Oral manifestations in acute lymphoblastic leukemic children under chemotherapy. *Journal of Clinical Pediatric Dentistry*, 32, 319-24.
19. Kenny, S. A. (1990). Effect of two oral care protocols on the incidence of stomatitis in hematology patients. *Cancer Nursing*, 13, 345-53.
20. McGuire, D. B., Fulton, J. S., Park, J., Brown, C. G., Correa, M. E., ...Eilers, J. (2013). Systematic review of the basic oral care for the management of oral mucositis in cancer patients. *Supportive Care in Cancer*, 21, 3165-77.
21. Harris, D. J., Eilers, J. G., Harriman, A., Cashavelly, B. J., & Maxwell, C. (2004). Putting Evidence into Practice: Evidence Based Intervention for the Management of Oral Mucositis. *Clinical Journal of Oncology Nursing*, 12, 80-96.
22. Farah, C.S., McIntosh, L., & McCullough, M. J. (2009). Mouthwashes. *Australian Prescriber*, 32, 162-4.